

REMARKS

In the Final Office Action, the Examiner rejected claims 22-42. By this paper, Applicants added new claims 43-53, and amended claims 22, and 25-42 for clarification of certain features to expedite allowance of the present application and to correct the claim numbering. These amendments do not add any new matter. Upon entry of these amendments and new claims, claims 22-53 will be pending in the present application and are believed to be in condition for allowance. In view of the foregoing amendments and the following remarks, Applicants respectfully request reconsideration and allowance of all pending claims.

Claim Objections

In the Final Office Action, the Examiner objected to the misnumbering of the claims. Specifically the Examiner stated:

The numbering of claims is not in accordance with 37 C.F.R. 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). For example, the amended claims recited two 28 and two 29's.

Misnumbered claims 28-40 have been renumbered 30-42.

Final Office Action, page 2. Applicants have amended the claims to correct the numbering as noted by the Examiner. Further, the new claims added after claim 42 start with number 43. In view of this amendment, Applicants respectfully request the Examiner withdraw the objection to the claims.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 32-39 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

Legal Precedent

First, regarding the written description requirement, the initial burden of proof regarding the sufficiency of the written description falls on the Examiner. Accordingly, the Examiner must present evidence or reasons why persons skilled in the art would not recognize a description of the claimed subject matter in the applicant's disclosure. *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (CCPA 1976).

A Diluent is an Example of an Excipient

In the Office Action, the Examiner specifically stated:

The claim(s) contains subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

New claim 32 recites a composition comprising: at least one of an excipients and a diluent; and a compound comprising: a tumor-seeking biomolecules; an intercalating moiety coupled to the tumor-seeking biomolecules and comprising acridine, porphyrin, ellipticine, phenantroline, carbozole, benzimidazole, or a compound that exhibits cytostatic activity; and a metal complexed with the intercalating moiety. However, while the specification teaches that the therapeutic composition comprise at least a suitable amount of a molecule in a diluent or excipients (paragraph 0016) (Emphasis added), the specification and claims, as originally filed, do not appear to have support for the limitation of at least one of excipients and a diluent. Applicant is invited to point to clear support or specific examples of the claimed limitation in the specification as-filed or remove such amendatory language in response to this action.

Final Office Action, pages 2-3. Applicants have amended claim 32 to state "A composition comprising: an excipient." Accordingly, the new matter rejection is believed to be moot. However, Applicants respectfully disagree with the Examiner's proposition that the composition may contain either an excipient or a diluent, but not both. Although the composition is not required to have both, it may have both.

As would be understood by one of ordinary skill in the art, active ingredients are generally not administered in a pure form to a patient. Any number of different compounds may typically be used in a pharmaceutical composition to stabilize the active ingredients, dilute the active ingredients to the appropriate concentration level, and carry other substances into the patient. These compounds are known as excipients. One specific type of excipient is a diluent. The use of the phrasing "diluent or excipient" in the application was not intended to indicate exclusivity, which would not make sense in this usage, but merely to state the generic class that a diluent would fall under. *See* Specification, paragraphs [0015]-[0017].

While claim 32 has been modified to recite "an excipient," one of ordinary skill in the art will recognize that this may include any number of substances, and, indeed, is likely to include a variety of substances to enhance or enable the pharmacological effects. For these reasons, Applicants respectfully note that while the rejection is moot under Section 112, first paragraph, the current claims are not limited to a single substance in combination with the active ingredient.

Claim Rejections under 35 U.S.C. § 102

In the Final Office Action, the Examiner rejected claims 22-24, 26-29, 32-37, and 40-42 under 35 U.S.C. § 102(b) as being anticipated by Toner et al. (WO 93/21957, hereinafter "Toner") as evidenced by Albert et al. (U.S. Patent No. 5,776,894, hereinafter "Albert"). Specifically, the Examiner stated, *inter alia*:

Toner et al. teach a targeting radioactive immunoreagent comprising a metal radionuclide ion, a complexing agent which is a derivative of phenantroline and an immunoreactive group covalently bonded through a protein reactive group to the complexing agent (page 6, lines 1-10 and page 8, lines 9-13, structure A-IV). With regards to the immunoreactive group, the WO document teaches that the immunoreactive group includes, but is not limited to, antibodies such as B72.3, 9.2.27, D612, UJ13A, NRLU-10, 7E11c5, CC49, TNT, PR1A3, ING-1, B174 and B43 antibodies (page 122).

Final Office Action, page 5. Applicants respectfully traverse this rejection.

Legal Precedent and Guidelines

The pending claims must be given an interpretation that is reasonable and consistent with the *specification*. See *In re Prater*, 415 F.2d 1393, 1404-05, 162 U.S.P.Q. 541, 550-51 (C.C.P.A. 1969) (emphasis added); see also *In re Morris*, 127 F.3d 1048, 1054-55, 44 U.S.P.Q.2d 1023, 1027-28 (Fed. Cir. 1997); see also M.P.E.P. §§ 608.01(o) and 2111. Indeed, the specification is “the primary basis for construing the claims.” See *Phillips v. AWH Corp.*, No. 03-1269, -1286, at 13-16 (Fed. Cir. July 12, 2005) (*en banc*). One should rely *heavily* on the written description for guidance as to the meaning of the claims. See *id.*

Interpretation of the claims must also be consistent with the interpretation that *one of ordinary skill in the art* would reach. See *In re Cortright*, 165 F.3d 1353, 1359, 49 U.S.P.Q.2d 1464, 1468 (Fed. Cir. 1999); M.P.E.P. § 2111. “The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation.” See *Collegenet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 75 U.S.P.Q.2d 1733, 1738 (Fed. Cir. 2005) (quoting *Phillips v. AWH Corp.*, 75 U.S.P.Q.2d 1321, 1326). The Federal Circuit has made clear that derivation of a claim term must be based on “usage in the ordinary and accustomed meaning of the words amongst artisans of ordinary skill in the relevant art.” See *id.*

Anticipation under section 102 can be found only if a single reference shows exactly what is claimed. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 U.S.P.Q. 773 (Fed. Cir. 1985). For a prior art reference to anticipate under section 102, every element of the claimed invention must be identically shown in a single reference. *In re Bond*, 910 F.2d 831, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). To maintain a proper rejection under section 102, a single reference must teach each and every limitation of the rejected claim. *Atlas Powder v. E.I. du Pont*, 750 F.2d 1569 (Fed. Cir. 1984). Accordingly, the Applicants need only point to a single element not found in the cited reference to demonstrate that the cited reference fails to anticipate the claimed subject matter. The prior art reference also must show the *identical* invention "*in as complete detail as contained in the ... claim*" to support a *prima facie* case of anticipation. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q. 2d 1913, 1920 (Fed. Cir. 1989).

Toner Does Not Disclose a Compound Having an Intercalating Moiety

Although Applicants do not intend or suggest that the specification of the present application should be read into the claims, the Applicants stress that the specification provides context and meaning to the present claims. The present application is directed to metal complexes having a moiety with an affinity for cancer cells (e.g., a tumor seeking molecule), an intercalating moiety that will insert between the base pairs in a strand of deoxyribonucleic acid (DNA), and a metal center bound to the moieties having the affinity for cancer cells and the intercalation moiety. *See* Specification, paragraphs [0008]-[0009]. The application specifically states that the "intercalating moiety will then insert into the DNA strand." Specification, paragraph [0009]. The application goes on to further describe the process for a radioactive nuclide's degradation of DNA, stating "when intercalating in one of the grooves, the probability to hit is very high since the nucleus is practically surrounded by DNA." Specification, paragraph [0019]. The most effective characteristics of a DNA intercalation moiety are also described in the specification, which states that "to provide a strong intercalation, the intercalator should be preferably planar and aromatic heterocyclic." Specification, paragraph [0019]; *see also id.*, paragraph [0037] and Fig. 2.

As one of ordinary skill in the art would recognize, the present specification's description of the intercalation moieties and their functionality is completely consistent with the well understood meaning of a DNA intercalating moiety. For example, a definition from a medical dictionary is provided in the attached Exhibit A. This definition was available well before the filing date of the present application, U.S. Serial No. 10/707,994, or its parent application, U.S. Serial No. 09/913,788, filed on Feb. 24, 2000. According to the dictionary, intercalation may be defined as "the process of insertion between two other entities; e.g., insertion of a dye or drug between stacked bases in DNA." STEDMAN'S MEDICAL DICTIONARY 880 (26th edition, 1995).

Accordingly, independent claims 22, 32, and 40 recite, *inter alia*, "a moiety having an affinity for cancer cells," and "an intercalating moiety coupled to the moiety having an affinity for cancer cells, wherein the intercalating moiety is configured to insert into the structure of deoxyribonucleic acid." (Emphasis added). The use of intercalating moieties to insert into the DNA strands of cancer cells is not taught by Toner.

Toner does teach a "metal radionuclide ion, a complexing agent which is pyridine, bipyridine, terpyridine, quarterpyridine, quinquepyridine, sexipyridine, or phenanthroline, and an immunnoreactive group covalently bonded through a protein reactive group to the complexing agent." Toner, page 6, lines 14-16. However, Toner specifically describes a large substituent on the complexing agent as a "protein reactive group." Toner, page 7, lines 24-25. This "protein reactive group" is not designed to insert into the DNA strands, as recited in the present claims, but is instead designed to react with "amine or sulfhydryl groups on the protein or biological molecule containing the immunoreactive group." Toner, page 15, lines 13-15. As stated by Toner, "especially preferred protein reactive groups include amino and isothiocyanato." *Id.* at page. 17, lines 14-15.

Further, although Toner does disclose a large class of possible compounds that may be used for the immunoreactive reagent, none of these are disclosed as reacting with DNA. *See* Toner, page 62, line 20-page 63, line 16. Instead, the targeting immunoreactive group of Toner is intended to bring the reagent into target cells. *See* Toner, page 63, line 18 - page 64, line 10. Indeed, one skilled in the art would recognize that if the immunoreactive reagent of Toner were to be replaced with a DNA intercalator, no specific targeting of cells would occur and broad toxicity may result.

As one skilled in the art would recognize, none of the structures 1-98 disclosed by Toner are "configured to insert into the structure of deoxyribonucleic acid," as recited by independent claims 22, 32, and 40. Thus, Toner does not teach or disclose all of the elements of these claims. In view of these deficiencies, among others, Toner cannot anticipate independent claims 22, 32, and 40. Further, Applicants respectfully assert that their respective dependent claims 23, 24, 26-29, 33-37, and 41-50 are allowable for at least the reasons discussed above, and for the further material contained therein. For at least these reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102 and allowance of these claims.

Claim Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claim 25 under 35 U.S.C. § 103(a) as being unpatentable over Toner in view of Albert. Further, the Examiner rejected claims 30-31 and 38-39 under 35 U.S.C. § 103(a) as being unpatentable over Toner in view of Holley et al. (Cancer Research 1992; 52: 4190-4195, hereinafter "Holley"). Applicants respectfully traverse these rejections.

Legal Precedent

The burden of establishing a *prima facie* case of obviousness falls on the Examiner. *Ex parte Wolters and Kuypers*, 214 U.S.P.Q. 735 (PTO Bd. App. 1979). In addressing obviousness determinations under 35 U.S.C. § 103, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (April 30, 2007), reaffirmed many of its precedents relating to obviousness including its holding in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). In *Graham*, the Court set out an objective analysis for applying the statutory language of §103:

Under §103, the scope and content of the prior art are to be determined, differences between the prior art and the claims at issue are to be ascertained, and the level of ordinary skill in the pertinent art are to be resolved. Against this background the obviousness or non-obviousness of the subject matter is to be determined. Such secondary considerations as commercial success, long-felt but unresolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *KSR, slip op.* at 2 (citing *Graham*, 383 U.S. at 17-18).

In *KSR*, the Court also reaffirmed that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 14. In this regard, the *KSR* court stated that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does ... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in

some sense, is already known.” *Id.* at 14-15. Traditionally, to establish a *prima facie* case of obviousness, the CCPA and the Federal Circuit have required that the prior art not only include all of the claimed elements, but also some teaching, suggestion, or motivation to combine the known elements in the same manner set forth in the claim at issue. *See, e.g., ASC Hospital Systems Inc. v. Montifiore Hospital*, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (holding that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching or suggestion supporting the combination.); *In re Mills*, 16 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 1990) (holding that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination). In *KSR*, the court noted that the demonstration of a teaching, suggestion, or motivation to combine provides a “helpful insight” in determining whether claimed subject matter is obvious. *KSR, slip op.* at 14. However, the court rejected a *rigid* application of the “TSM” test. *Id.* at 11. In this regard, the court stated:

The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and explicit content of issued patents. The diversity of inventive pursuit and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. *Id.* at 15.

In other words, the *KSR* court rejected a rigid application of the TSM test which requires that a teaching, suggestion or motivation to combine elements in a particular manner must be explicitly found in the cited prior art. Instead, the *KSR* court favored a more expansive view of the sources of evidence that may be considered in determining an apparent reason to combine known elements by stating:

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art all in order to determine whether there

was an apparent reason to combine in the known elements in the fashion claimed in the patent at issue. *Id.* at 14.

The *KSR* court also noted that there is not necessarily an inconsistency between the idea underlying the TSM test and the *Graham* analysis, and it further stated that the broader application of the TSM test found in certain Federal Circuit decisions appears to be consistent with *Graham*. *Id.* at 17-18 (citing *DyStar Textilfarben GmbH and Co. v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (2006) (“Our suggestion test is in actuality quite flexible and not only permits but *requires* consideration of common knowledge and common sense”); *Alza Corp. v. Mylan Labs, Inc.*, 464 F.3d 1286, 1291 (2006) (“There is flexibility in our obviousness jurisprudence because a motivation may be found *implicitly* in the prior art. We do not have a rigid test that requires a teaching to combine ... “)).

Furthermore, the *KSR* court did not diminish the requirement for objective evidence of obviousness. *Id.* at 14 (“To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.”); *see also, In re Lee*, 61 U.S.P.Q.2d 1430, 1436 (Fed. Cir. 2002) (holding that the factual inquiry whether to combine references must be thorough and searching, and that it must be based on *objective evidence of record*).

Further, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983); M.P.E.P. § 2145. Moreover, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified,

then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (CCPA 1959); *see* M.P.E.P. § 2143.01(VI). If the proposed modification or combination would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); *see* M.P.E.P. § 2143.01(V).

Toner and Albert Fail to Teach or Suggest an Intercalating Agent.

Turning to the claims, present independent claim 22 recites, *inter alia*, “a moiety having an affinity for cancer cells,” and “an intercalating moiety coupled to the moiety having an affinity for cancer cells, wherein the intercalating moiety is configured to insert into the structure of deoxyribonucleic acid.” (Emphasis added). As discussed above with respect to the rejections under 35 U.S.C. §102, Toner does not disclose an intercalating agent. Further, Albert does not obviate the deficiency of Toner.

In contrast to the recitations in claim 22, Albert teaches a somastatin peptide having a chelating group capable of complexing a metal, which may or may not be radioactive. *See* Albert, column 1, lines 36-47. These somastatin based compounds may be used for the treatment or diagnosis of various conditions. *See* Albert, column 1, lines 33-36. However, Albert does not teach or suggest any compounds “configured to insert into the structure of deoxyribonucleic acid.” as recited by claim 22. (Emphasis added). Thus neither Toner nor Albert, alone or in hypothetical combination, teaches all of the elements of independent claim 22.

Accordingly, as claim 25 depends from claim 22, it is allowable for at least the reasons discussed above, and for the further patentable material contained therein. For at least these reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103, and allowance of claim 25.

Toner and Holley Fail to Teach or Suggest an Intercalating Agent.

The Examiner rejected claims 30-31, 38, and 39 as being obvious over Toner in view of Holley. As previously discussed, Toner does not disclose an intercalating agent. Further, Holley does not obviate the deficiency of Toner.

In contrast to the present claims, Holley teaches a compound that cross-links DNA. See Holley, page 4192, in the first full paragraph of the Results section. This interaction is through reaction with the DNA (e.g., alkylation), and not through DNA intercalation. See *id.* at page 4193, in the first full paragraph of the Discussion section; see also, *id.* at page 4194, top left paragraph. Thus, Holley does not obviate the deficiencies of Toner

Further, as noted in the legal precedent section, if the proposed combination would change the principal of operation of prior art invention being modified, the teachings of the references are insufficient to render the claims *prima facie* obvious. As the cross-linking compounds of Holley would provide the opposite effect to that of the radionuclide of Toner, which would break a DNA strand, it would not have been obvious to combine the teachings of Holley with those of Toner. Although not discussed in Toner, which has no mention of DNA, the effect of a radionuclide in severing a DNA strand is discussed at length in the present application and demonstrated by Example 2. See Specification, paragraphs [0009], [0091]-[0095], and [0101]-[0104].

Thus, neither Toner nor Holley, alone or in hypothetical combination, teaches all of the elements of independent claims 22 and 32. Accordingly, as claims 30-31, 38, and 39 depend from claims 22 and 32, respectively, they are allowable for at least the reasons as discussed above, and for the further patentable material contained therein. For at least these reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103, and allowance of claim 30-31, 38, and 39.

New Claims

Applicants have added new dependent claims 43-50, 52, and 53, and new independent claim 51 to the present application to further define and claim aspects of the present invention. No new matter is added by way of these claims. Support for new dependent claims 43, 45, 47, and 49 may be found in the specification at least at page 8, paragraph [0036] and Figs. 2 and 3. Support for new dependent claims 44, 46, 48, and 50 may be found in the specification at least at page 4, paragraph [0010]. Further, as these claims depend from independent claims 22 and 32, respectively, they are allowable over the presently cited art for at least the reasons discussed above, and for the additional material claimed therein.

New independent claim 51 and new dependent claims 52 and 53 are allowable for at least the same reasons as claim 22. Support for new independent claim 51 may be found in the specification at least at page 4, paragraphs [0008]-[0010]; page 8, paragraph [0036]; and in Fig. 2. Support for new dependent claim 52 may be found at least at page 3, paragraph [0006]. Support for new dependent claim 53 may be found at least at page 4, paragraph [0010].

Claim Rejections under Doctrine of Obviousness-Type Double Patenting

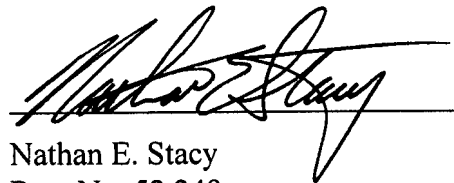
In the Final Office Action, the Examiner rejected claims 22 and 32 under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 6,844,425, which is the parent of the present continuing application. Although Applicants do not necessarily agree with the Examiner's assertion, Applicants may be amenable to filing a terminal disclaimer upon allowance of the claims in the present application. Accordingly, Applicants respectfully request that the Examiner hold in abeyance the double-patenting rejection until the present claims are determined to be allowable.

Conclusion

Applicants respectfully submit that all pending claims should be in condition for allowance. However, if the Examiner believes certain amendments are necessary to clarify the present claims or if the Examiner wishes to resolve any other issues by way of a telephone conference, the Examiner is kindly invited to contact the undersigned attorney at the telephone number indicated below.

Respectfully submitted,

Date: June 26, 2007

A handwritten signature in black ink, appearing to read "Nathan E. Stacy", is written over a horizontal line.

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